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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,153	04/05/2006	Robert Jordan	056440-1402	9124

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KRAMER LEVIN NAFTALIS & FRANKEL LLP  
INTELLECTUAL PROPERTY DEPARTMENT  
1177 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036

EXAMINER
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BIANCHI, KRISTIN A

ART UNIT	PAPER NUMBER
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1626

NOTIFICATION DATE	DELIVERY MODE
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09/14/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/561,153	<b>Applicant(s)</b> JORDAN ET AL.	
	<b>Examiner</b> KRISTIN BIANCHI	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 June 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-45 is/are pending in the application.
- 4a) Of the above claim(s) 3, 16-19 and 23-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-15 and 20-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/16/2005, 03/27/2006, 04/04/2008 and 06/25/2009</u> .       | 6) <input type="checkbox"/> Other: _____                          |



### **DETAILED ACTION**

Claims 1-45 are currently pending in the instant application. Claims 3, 16-19 and 23-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected subject matter. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference which anticipates one group would not render obvious the other. Claims 1, 2, 4-15, and 20-22 are rejected.

#### ***Information Disclosure Statements***

The information disclosure statements filed on December 16, 2005, March 27, 2006, April 4, 2008, and June 25, 2009 were considered and signed copies of form 1449 are enclosed herewith.

#### ***Election/Restrictions***

Applicants' election without traverse of Group I, namely claims 1, 2, 4-17, and 20-27, in the response filed on June 11, 2009 has been acknowledged.

Examiner sincerely apologizes, but a mistake was made in the grouping of the claims disclosed in the Office Action dated May 12, 2009. Upon further consideration, the claims drawn to pharmaceutical compositions (i.e., claims 16, 17 and 23-27) should have been grouped with the claims drawn to compounds (i.e., Groups IV-VI) and *not* with claims drawn to methods of using the compounds (Groups I-III). The groups of inventions are now:

Group I, claims 1, 2, 4-15, and 20-22, drawn to a method of using a compound of formula Ia.

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Group II, claims 1, 3, 4, 7-15, 20, and 21, drawn to a method of using a compound of formula Ib.

Group III, claims 1, 4-15, 20, and 21, drawn to a method of using a compound of the formula disclosed in claim 1 other than compounds of formula Ia and Ib.

Group IV, claims 16-19 and 23-28, drawn to a compound and a pharmaceutical composition comprising a compound of formula Ia.

Group V, claim 16-18 and 23-27, drawn to a compound and a pharmaceutical composition comprising a compound of formula Ib.

Group VI, claims 16-19 and 23-27, drawn to a compound of the formula disclosed in claim 18 and a pharmaceutical composition comprising a compound of the formula disclosed in claim 16 other than compounds of formula Ia and Ib.

Group VII, claims 29-35, drawn to a method of making a compound of formula I(a).

Group VIII, claims 36-42, drawn to a method of making 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide.

Group IX, claims 43-45, drawn to a method of making 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide.

The restriction requirement is still deemed proper and is hereby maintained (i.e., claims 1, 2, 4-15, and 20-22 of elected Group I were searched and examined).

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-15, and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one

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skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)).

These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

***The state of the prior art and the predictability or lack thereof in the art***

The term "prevention" actually means to anticipate or counter in advance, to keep from happening, etc. and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "preventative" effect.

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e., what compounds can treat which specific disease or condition by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be

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individually assessed for physiological activity. In *re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects, whether or not the infection caused by an orthopox virus is affected by the administration of a compound of formula Ia would make a difference.

***The amount of direction or guidance present and the presence or absence of working examples***

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will possess the alleged activity. The only direction or guidance present in the instant specification is the list of viruses which fall within the orthopox genus (i.e., pages 1 and 5), the *in vitro* CPE inhibition assays and the corresponding EC50 values (i.e., pages 35-39). However, the CPE inhibition assay does not directly measure virus replication inhibition. Applicants' specification even mentions that it is theoretically possible to inhibit CPE without inhibiting virus replication (i.e., page 5). In other words, the specification does not contain any evidentiary support that the compounds of formula Ia would be able to treat or prevent an infection caused by an orthopox virus. Furthermore, there are no working examples to support the treatment or prevention of the instantly claimed infections.

The uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical

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development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of *in vivo* use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of *in vivo* success for any additional diseases or conditions that may still be embraced in response to this action. See MPEP 2164.05(a).

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds and pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

#### ***The level of skill in the art***

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or conditions would benefit from this activity.

Thus, the specification fails to provide sufficient support of the use of the compounds of the instant claims for the prevention or treatment of an infection caused by an orthopox virus, as a result necessitating one of skill to perform an exhaustive search for which orthopox viruses can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention.

***The quantity of experimentation needed***

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which specific orthopox viruses are benefited by the administration of the compounds of the instant claims and would furthermore have to determine which of the claimed compounds are beneficial.

Factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the chemical nature of the invention and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which specific orthopox viruses can be treated or prevented by the compounds encompassed in the instant claims, with no assurance of success.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed/

Kristin Bianchi

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Primary Examiner, Art Unit 1626

Examiner  
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